

REMARKS

Claims 1-41 are pending in the application. Claims 3, 5, 8-18, 24, 25, and 27-41 were previously withdrawn from consideration. Claims 1 and 7 are currently amended. Claims 3, 5, 8-18, 24, 25, 27-41 have been cancelled without prejudice. New Claims 42-48 are presented here. Thus, Claims 1, 2, 4, 6, 7, 19-23, 26, and 42-48 are currently presented for examination. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 currently stand rejected.

Support for the amendments to pending claims and new claims presented herein is found in the original claims as filed and throughout the specification, in particular on page 4 at lines 14-17, page 10 at lines 5-7, page 14 at lines 1-7, page 16 at lines 1-8, in Examples 10 and 11, and in Figures 53 to 55. The amendments to pending claims and new claims presented herein do not introduce new matter.

Applicants thank the Examiner for withdrawing prior claim rejections under 35 USC §102(b) and 35 USC §103 in the Final Office Action mailed August 2, 2006.

New Claim Rejections in Final Office Action mailed August 2, 2006

Claim Rejections under 35 USC §103 over Müller et al., WO 97/01580, and Shu et al.

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, and 26 stand rejected under 35 U.S.C. §103 over Müller et al., as evidenced by WO 97/01580 in view of Shu et al. (1995). According to the Office Action (OA), Müller et al. discloses a multifunctional compound comprising fully functional heterodimers, but does not disclose a non-immunoglobulin portion having receptor or ligand function. Shu et al. allegedly discloses making and using a non-immunoglobulin portion having receptor or ligand function. WO 97/10580 is cited as a supporting document.

Prima facie obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. See, MPEP §§ 2142, 2143

Cited references do not teach the claimed invention.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03, citing *In re Royka*, 180 USPQ 580 (CCPA 1974). Here, the claims recite multifunctional compounds having two polypeptide chains, wherein one polypeptide chain includes the constant CHI-domain of an

immunoglobulin heavy chain and the other polypeptide chain includes the constant CL-domain of an immunoglobulin light chain, and the polypeptide chains further include, fused to the constant domains, at least three polypeptide functional domains having different receptor or ligand functions, wherein at least one the functional domains is a non-immunoglobulin portion having receptor or ligand function, and further wherein at least two of the different functional domains lack an intrinsic affinity for one another and the polypeptide chains are linked via the immunoglobulin constant domains.

Müller *et al.* discloses “bispecific miniantibodies” and does not disclose a multifunctional compound having at least *three* polypeptide functional domains having different receptor or ligand functions fused to constant domains, wherein at least one of the functional domains is a non-immunoglobulin portion having receptor or ligand function. Shu *et al.* discloses a single-chain fusion protein SCIg-IL-2 that forms a homodimer formed by linking identical polypeptide chains by disulfide bonds in the hinge region, wherein each polypeptide chain has a VH-VL functional domain derived from the CC49 antibody fused to C2 and IL-2 fused to C3. Shu *et al.* does not disclose the use of CH1 or CL, the formation of heterodimers via the CH1 and CL constant domains, or a heterodimeric multifunctional compound having at least *three* polypeptide functional domains having different receptor or ligand functions fused to constant domains. Combining the disclosures of Müller *et al.* and Shu *et al.*, does not teach or suggest the claimed invention and therefore, no *prima facie* case of obviousness has been established.

No motivation to combine or modify the references

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP §2143.01. Neither reference contains such a teaching, suggestion, or motivation to produce the claimed invention. In particular, the secondary reference Shu *et al.* does not contain a teaching, suggestion, or motivation to modify the primary reference Müller *et al.* to produce the claimed invention.

As discussed above, Müller *et al.* discloses a heterodimeric “bispecific miniantibody” with two functional domains and admittedly does not teach or suggest functional domains including a non-immunoglobulin portion as in the claimed invention. The disclosure in Shu *et al.* is limited to a single-chain fusion protein SCIg-IL-2 that forms a homodimer of two identical polypeptide chains linked by disulfide bonds in the hinge region, and fails to teach or suggest a heterodimeric multifunctional compound having at least *three* polypeptide

functional domains having different receptor or ligand functions fused to constant domains. Finally, Shu *et al.* fails to teach or suggest how or why to modify Müller *et al.* to produce the claimed invention. Because no teaching, suggestion, or motivation to combine or modify the teachings of Müller *et al.* and Shu *et al.* to produce the claimed invention is found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, no *prima facie* case of obviousness has been established.

Because no *prima facie* case of obviousness has been established, the claim rejections under 35 USC §103 over Müller *et al.*, and Shu *et al.* are improper and should be withdrawn

Claim Rejections under 35 USC §103 over Müller et al., Shu et al., and Plückthun and Pack

Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23 and 26 stand rejected under 35 U.S.C. §103(a) over Müller *et al.* in view of Shu *et al.*, and further in view of Plückthun and Pack. According to the Office Action, Müller *et al.* discloses a multifunctional compound comprising two monomers, but admittedly does not disclose a non-immunoglobulin portion having receptor or ligand function, or using the upper hinge region of human IgG3. Shu *et al.* is cited for allegedly teaching making and using a non-immunoglobulin portion having receptor or ligand function. Plückthun and Pack is cited for allegedly disclosing the use of the upper hinge region from human IgG3. It is argued that it would have been obvious to substitute the linkers of Müller *et al.* with the upper hinge region of human IgG3 taught by Plückthun and Pack, with an expectation of success because each reference allegedly teaches how to make each element of the claimed invention.

First, the rejection of Claims 1, 2, 4, 6, 7, 19-22, and 26 are over the cited references is improper because these claims do not recite the upper hinge region of human IgG.

Second, the claim rejections under 35 USC §103 are improper because no *prima facie* case of obviousness has been established.

The criteria for establishing a *prima facie* case of obviousness is presented above. As discussed above, the combination of Müller *et al.* and Shu *et al.* does not teach the claimed invention, and there is no teaching, suggestion, or motivation to modify Müller *et al.* and Shu *et al.* to make the claimed invention. Substituting the linkers disclosed in Müller *et al.* with the upper hinge region of human IgG3 disclosed in Plückthun and Pack does not produce the claimed invention and fails to cure the deficiency of the rejection. We conclude that no *prima facie* case of obviousness has been established and the rejection under 35 USC §103 should be withdrawn.

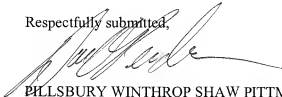
CONCLUSION

Claims 1-41 are pending in the application. Claims 3, 5, 8-18, 24, 25, and 27-41 were previously withdrawn from consideration. Claims 1 and 7 are currently amended. Claims 3, 5, 8-18, 24, 25, 27-41 have been cancelled without prejudice. New Claims 42-48 are presented here. Thus, Claims 1, 2, 4, 6, 7, 19-23, 26, and 42-48 are currently presented for examination. Claims 1, 2, 4, 6, 7, 19, 20, 21, 22, 23, and 26 currently stand rejected.

Applicants respectfully request that the claim amendments be entered and that Claims 1, 2, 4, 6, 7, 19-23, 26, and 42-48 be found in condition for allowance.

Because this paper is being submitted within two months of the mailing date of Notice of Appeal filed January 26, 2007, Applicants believe no fees are due. If any fees are due, please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any overpayments to the above-referenced Deposit Account.

Respectfully submitted,



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